



PATENT  
Docket No. 249.0002 0101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Dominic E. COSGROVE ) Group Art Unit: 1641  
Serial No.: 09/970,318 )  
Confirmation No.: 1885 ) Examiner: Nelson C. YANG  
Filed: 03 October 2001 )  
For: IMMUNODIAGNOSTIC DETERMINATION OF USHER SYNDROME TYPE  
IIA

DECLARATION UNDER 37 C.F.R. §1.132  
OF DOMINIC E.COSGROVE

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

I, Dominic E. Cosgrove, declare and say as follows:

1. I am the inventor of the subject matter claimed in the above-identified U.S. Patent Application Serial No. 09/970,318, filed October 3, 2001.
  
2. I, Dominic E. Cosgrove, received a Ph.D. in Biochemistry from the University of Nebraska Medical Center, Omaha, Nebraska, in 1989 and a B.A. in Life Science from the University of Nebraska-Lincoln, Lincoln, Nebraska, in 1984. Since 1991 I have been the Coordinator of the Gene Expression Laboratory, Center for Hereditary Communication Disorders, Boys Town National Research Hospital, Omaha, Nebraska. Since 1996 I have been a Staff Scientist III with the Center for Hereditary Communication Disorders, Boys Town National Research Hospital. Since 1998 I have been an Associate Professor in the Department of Biomedical Sciences at Creighton University School of Medicine, Omaha, Nebraska. From 1998 to 2002 I was an Associate Professor of Otolaryngology and Human Communication, Creighton University School of Medicine and from 1991 to

**Declaration Under 37 C.F.R. § 1.132 of Dominic E. COSGROVE****Page 2**

Serial No.: 09/970,318

Filed: 03 October 2001

For: IMMUNODIAGNOSTIC DETERMINATION OF USHER SYNDROME TYPE IIA

---

1998 I was an Assistant Professor of Otolaryngology and Human Communication and Biomedical Research at Creighton University School of Medicine. My research activities have included extensive work on the genetic and molecular aspects of various genetic diseases, including Alport syndrome and Usher's syndrome type IIa. I have more than 27 peer-reviewed publications on these and other related topics.

3. I have read and am familiar with the Office Action mailed on January 24, 2005 with respect to the above-identified application and make this Declaration in support of the patentability of the claims of U.S. Patent Application Serial No. 09/970,318.
4. To determine the feasibility of diagnosing Usherin syndrome type IIa using purified usherin antibody, my laboratory carried out immunohistochemical staining for usherin in basement membrane of minor salivary gland tissue from five subjects with confirmed Usher syndrome type IIa. Archival minor salivary gland tissue samples from patients without Usher syndrome were used as controls. The results are published in Cohn et al., Laryngoscope, 2004 114(7):1310-4, "Immunohistochemistry and reverse transcriptase-polymerase chain reaction as methods for diagnostic determination of usher syndrome type IIa."
5. Antibodies specific for usherin were developed by immunizing rabbits with the entire LN domain (amino acids 318 to 518) of human usherin (corresponding to SEQ ID NO:2 of present U.S. Patent Application Serial No. 09/970,318) expressed using the FLAG-ATS system (Sigma, St. Louis, MO, USA). This antibody is referred to as Antibody 2 in present U.S. Patent Application Serial No. 09/970,318 (see page 22, lines 19-30 of the specification of U.S. Patent Application Serial No. 09/970,318).
6. Figure A below shows normal salivary glands immunostained with antibodies specific for either usherin or type IV collagen. Hematoxylin and eosin (H&E) staining is provided

**Declaration Under 37 C.F.R. § 1.132 of Dominic E. COSGROVE**

Page 3

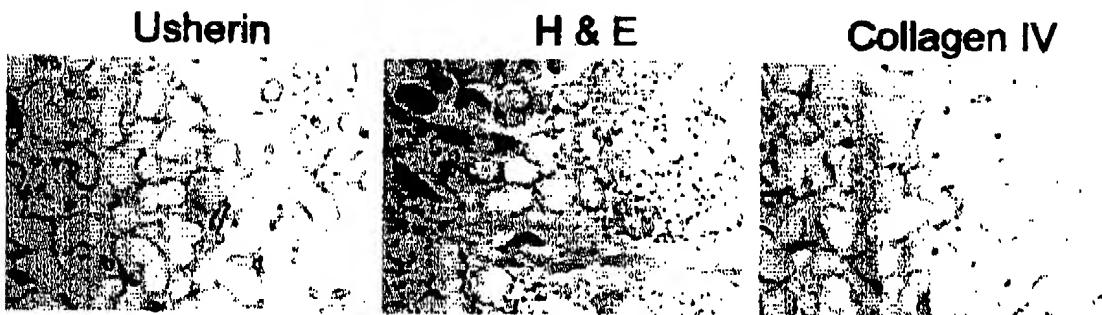
Serial No.: 09/970,318

Filed: 03 October 2001

For: IMMUNODIAGNOSTIC DETERMINATION OF USHER SYNDROME TYPE IIA

---

for tissue visualization. Materials and methods are as detailed in Cohn et al., Laryngoscope, 2004 114(7):1310-4. Figure A demonstrates that usherin is present in the basement membranes of salivary gland tissue from normal individuals and co-localizes with collagen.

**Figure A**

7. Figure B below shows the absence of usherin immunostaining in cryosections of minor salivary glands from a patient with Usher syndrome type IIa homozygous for the 2299 mutation. Cryosections of minor salivary glands were immunostained using antibodies specific for usherin or type IV collagen. Four additional individuals were tested with similar results. Again, materials and methods are as detailed in Cohn et al., Laryngoscope, 2004 114(7):1310-4.

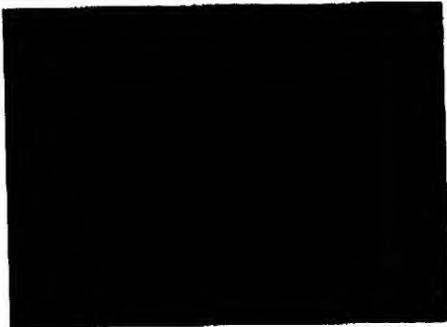
Page 4

**Declaration Under 37 C.F.R. § 1.132 of Dominic E. COSGROVE**

Serial No.: 09/970,318

Filed: 03 October 2001

For: IMMUNODIAGNOSTIC DETERMINATION OF USHER SYNDROME TYPE IIA

**USHERIN****Collagen IV****Exhibit B**

8. I submit that one skilled in the art would conclude from the data in Exhibits A and B that antibodies immunoreactive with human usherin can be used to successfully diagnose Usher syndrome type IIa in an individual.
  
9. I further declare that statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date:

4-22-05

Dominic E. Cosgrove

A handwritten signature in black ink, appearing to read "Dominic E. Cosgrove", is written over the printed name below it.



PATENT  
Docket No. 249.0002 0101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Dominic E. COSGROVE ) Group Art Unit: 1641  
  )  
Serial No.: 09/970,318               ) Examiner: Nelson C. YANG  
Confirmation No.: 1885               )  
  )  
Filed: 03 October 2001              )  
  )  
For: IMMUNODIAGNOSTIC DETERMINATION OF USHER SYNDROME TYPE  
IIA

---

**DECLARATION UNDER 37 C.F.R. §1.132**  
**OF DOMINIC E.COSGROVE**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

I, Dominic E. Cosgrove, declare and say as follows:

1. I am the inventor of the subject matter claimed in the above-identified U.S. Patent Application Serial No. 09/970,318, filed October 3, 2001.
  
2. I, Dominic E. Cosgrove, received a Ph.D. in Biochemistry from the University of Nebraska Medical Center, Omaha, Nebraska, in 1989 and a B.A. in Life Science from the University of Nebraska-Lincoln, Lincoln, Nebraska, in 1984. Since 1991 I have been the Coordinator of the Gene Expression Laboratory, Center for Hereditary Communication Disorders, Boys Town National Research Hospital, Omaha, Nebraska. Since 1996 I have been a Staff Scientist III with the Center for Hereditary Communication Disorders, Boys Town National Research Hospital. Since 1998 I have been an Associate Professor in the Department of Biomedical Sciences at Creighton University School of Medicine, Omaha,

Serial No.: 09/970,318

Filed: 03 October 2001

For: IMMUNODIAGNOSTIC DETERMINATION OF USHER SYNDROME TYPE II A

---

Nebraska. From 1998 to 2002 I was an Associate Professor of Otolaryngology and Human Communication, Creighton University School of Medicine and from 1991 to 1998 I was an Assistant Professor of Otolaryngology and Human Communication and Biomedical Research at Creighton University School of Medicine. My research activities have included extensive work on the genetic and molecular aspects of various genetic diseases, including Alport syndrome and Usher's syndrome type IIa. I have more than 27 peer-reviewed publications on these and other related topics.

3. I have read and am familiar with the Office Action mailed on January 24, 2005 with respect to the above-identified application and make this Declaration in support of the patentability of the claims of U.S. Patent Application Serial No. 09/970,318.
4. To determine the feasibility of diagnosing Usherin syndrome type IIa using purified usherin antibody, my laboratory carried out immunohistochemical staining for usherin in basement membrane of minor salivary gland tissue from five subjects with confirmed Usher syndrome type IIa. Archival minor salivary gland tissue samples from patients without Usher syndrome were used as controls. The results are published in Cohn et al., Laryngoscope, 2004 114(7):1310-4, "Immunohistochemistry and reverse transcriptase-polymerase chain reaction as methods for diagnostic determination of usher syndrome type IIa."
5. Antibodies specific for usherin were developed by immunizing rabbits with the entire LN domain (amino acids 318 to 518) of human usherin (corresponding to SEQ ID NO:2 of present U.S. Patent Application Serial No. 09/970,318) expressed using the FLAG-ATS system (Sigma, St. Louis, MO, USA). This antibody is referred to as Antibody 2 in

Serial No.: 09/970,318

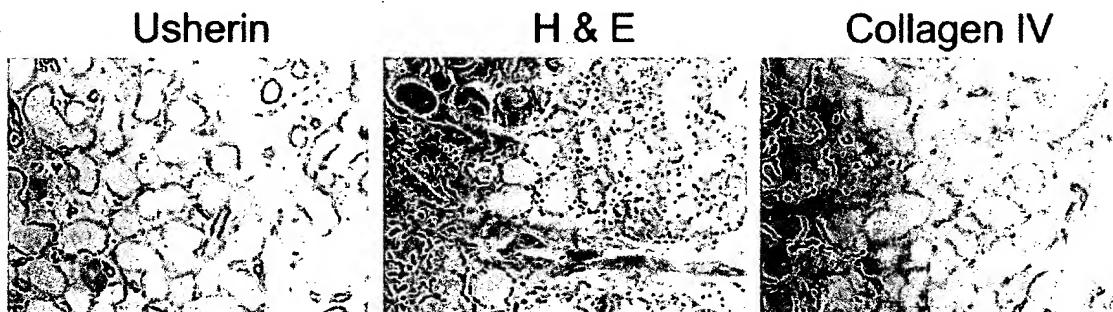
Filed: 03 October 2001

For: IMMUNODIAGNOSTIC DETERMINATION OF USHER SYNDROME TYPE IIA

---

present U.S. Patent Application Serial No. 09/970,318 (see page 22, lines 19-30 of the specification of U.S. Patent Application Serial No. 09/970,318).

6. Figure A below shows normal salivary glands immunostained with antibodies specific for either usherin or type IV collagen. Hematoxylin and eosin (H&E) staining is provided for tissue visualization. Materials and methods are as detailed in Cohn et al., Laryngoscope, 2004 114(7):1310-4. Figure A demonstrates that usherin is present in the basement membranes of salivary gland tissue from normal individuals and co-localizes with collagen.



**Figure A**

7. Figure B below shows the absence of usherin immunostaining in cryosections of minor salivary glands from a patient with Usher syndrome type IIa homozygous for the 2299 mutation. Cryosections of minor salivary glands were immunostained using antibodies specific for usherin or type IV collagen. Four additional individuals were tested with similar results. Again, materials and methods are as detailed in Cohn et al., Laryngoscope, 2004 114(7):1310-4.

**Declaration Under 37 C.F.R. § 1.132 of Dominic E. COSGROVE**

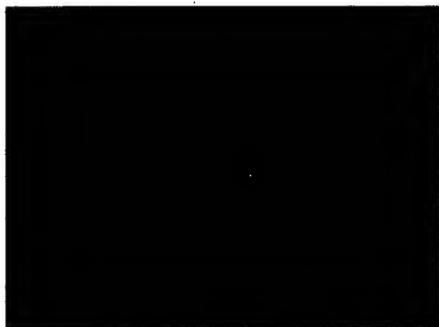
Page 4

Serial No.: 09/970,318

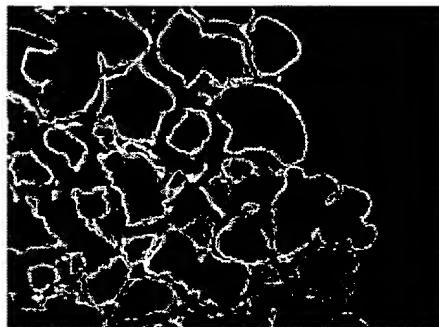
Filed: 03 October 2001

For: IMMUNODIAGNOSTIC DETERMINATION OF USHER SYNDROME TYPE IIA

---



USHERIN



Collagen IV

**Figure B**

8. I submit that one skilled in the art would conclude from the data in Figures A and B that antibodies immunoreactive with human usherin can be used to successfully diagnose Usher syndrome type IIa in an individual.
  
9. I further declare that statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: \_\_\_\_\_

Dominic E. Cosgrove